# The Science and Business of COVID-19 Webinar Series

## Webinar Highlights

**Webinar**

### Preventing & Treating COVID-19: When Will We Get a Vaccine? Are There Any Effective Treatments?

**20 April 2020 (Mon) | 12.30pm - 1.30pm (SGT)**

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## Introduction

A joint effort of the SingHealth Duke-NUS Global Health Institute (SDGHI), Saw Swee Hock School of Public Health (SSHSPH) and the American Chamber of Commerce (AmCham) in Singapore, The Science and Business of COVID-19 Webinar Series draws on expertise located across these organizations and brings together other international experts to provide a rich multidisciplinary discussion across the public and private sectors. Through this Series, the connection between medicine and science to economic and business interests will be explored – where possible, strategies that can be adopted by businesses to be better prepared will be outlined.

In the second session, the experts shared more about the process for vaccine development from the "prototype" identification to the end goal of global immunization. The options in therapeutics was also discussed in depth, which include the process of evaluating its safety and efficacy, and ensuring its access and availability. The road map of key activities and expected timeline were also be discussed in this session.

You can access the recording of the webinar here.

## Broad Overview of the COVID-19 Outbreak in Singapore

The first COVID-19 case in Singapore was detected on 23rd January this year; and the current 'circuit breaker' was introduced on 7th April.

As of 20th April, more than 6,000 cases have been detected in Singapore.

- About 95% of new cases are due to transmissions amongst foreign workers residing in dormitories, whilst the remaining 5% are largely comprised of local and permanent residents.
- Hardly any import cases due to the current travel restrictions.

There are 11 reported fatalities, and a low overall case fatality rate (0.167%).

- Re: COVID-19 disease severity is highly associated with age, but the current patient cohort largely consists of young migrant workers with few comorbidities.
- Therefore, Singapore's low mortality rate is likely to have more to do with the unique demographic case mix at this point in time plus the early detection of cases, both of which limits the risk for severe illness.
- Need to caution against complacency.

Majority of patients who have required ICU care have since recovered – only 6 fatalities out of > 90 ICU cases.

This is indicative of the reasonably good health outcomes achieved by a high standard of care alone, but it also poses challenges in terms of our approach to therapeutic interventions.

## Drug Therapies

There are no proven effectiveness in any of the proposed antivirals, immune modulators or steroid drugs so far.

A lot of focus is currently being put on Remdesivir. Unfortunately, at this point in time, there are no good data to support its use. Current trial data from Gilead Sciences is contradictory at best; and there is a lack of control arms as well, making data interpretation and comparison very difficult.

Hydroxychloroquine and chloroquine – most reports are observational and many trials are not well-randomized. Many trial sites have also terminated the use of chloroquine as a therapeutic agent due to higher reported toxicities.

Hence, this drives home the point that whilst experimentation is important, researchers must be extremely careful in monitoring these unproven therapeutic options. Ultimately, we must first seek to 'Do no harm'.

Furthermore, as mentioned earlier, good supportive and ICU care alone have already achieved reasonably good clinical outcomes. More than 80% of patients have conditions that are mild to moderate and self-limiting; and only a small proportion of them will require supplementary oxygen and ICU care.

Therefore, it can be challenging for clinicians to initiate therapeutic treatments of no proven efficacy.

## Reinfections and Herd Immunity

The term "reinfection" might be misleading, because there isn't enough clinical evidence to suggest that it is indeed another separate episode of infection. Some hypotheses:

- Polymerase Chain Reaction (PCR) tests – the primary method of COVID-19 diagnosis – can be very sensitive and may erroneously pick up false-positive results.
- Viral shedding can be quite prolonged and intermittent – therefore, having two negative PCR tests followed by a positive test cannot by itself equate to a new infection.
- For acute viral respiratory infections like COVID-19, respiratory symptoms may persist for prolonged periods of time, and may even appear to be worsened sometimes. For example, some COVID-19 patients have experienced an exacerbation of their cough symptoms following hospital discharge, but upon re-examination, no clinical evidence of reinfection was found.

Herd immunity – a well-known phenomenon for many viral conditions where once a certain level of immunity is reached in the community, transmissions can be slowed or stopped due to the new lack of susceptible individuals.

- Its potential for use as an epidemic control measure is dependent on our understanding of reinfection issues, including its possibility, longevity of acquired immunity etc.

At this point in time, many factors pertaining to both issues are still unclear, hence more research will have to go into this area for us to develop a conclusive view on this.

## Vaccine Development: Background, Current Strategies

There are two aims to vaccination: to create personal protection and herd immunity.

In general, vaccines function by giving the immune system a glimpse of a pathogen to allow the immune system to recognize it as foreign material and develop a memory response (both antibody and T-cell).

Most good vaccines are around 60 to 80% protective, and so that's what we will be targeting for as well with SARS-CoV-2 vaccine candidates.

Current vaccine strategies under consideration:

- Most researchers are looking into virus-like particles (VLPs), which are particles that replicate the whole structure of the virus from its nucleic acid to surface proteins.
- There are also nucleic acid-based vaccines such as DNA and RNA vaccines; as well as subunit vaccine formulations which usually require the use of adjuvants to trigger an immune response.
- For safety reasons, live-attenuated vaccines are not really the prime targets here.

Vaccine development also involves the optimization of the dosages of the vaccine and its schedule to achieve durable protection. Additional studies will be necessary to determine what is most effective for each individual vaccine candidate.

That said, until a vaccine or antiviral drug becomes available, current public health control measures will continue to form the mainstay in our current battle to reduce disease transmission. The importance of simple control measures such as hand hygiene and social distancing sensibilities cannot be underestimated.

## Vaccine Development: Why Are There So Many Different Efforts to Develop a Vaccine, and Is That Necessarily a Good Thing?

Globally, there are about 70 ongoing vaccine efforts for the SARS-CoV-2 virus with 30 to 40 coming onto the scene.

This begs the question – are these really needed? Are we just trying to race with each other and see who wins?

No, it is not an ego race. To win this coronavirus battle, we need to try multiple strategies and take multiple shots at goal.

We've only had around 5 months to study this virus – there is a lot that we don't know about it. Hence, there is no basis to claim that one vaccine candidate is going to work better than another.

There is also potential for multiple vaccine candidates to serve different populations in the long run, according to their respective safety benefits. For example, in the case of flu vaccines – live-attenuated vaccines are given to younger populations, whilst subunit vaccines are given to the elderly. The latter may not be quite as effective, but it is a little safer for use amongst elderly.

## Vaccine Development: How Long Will It Take? How Can We Do It?

We know a lot more about vaccine science today as compared to the past.

A lot of the things that we do today in vaccine development are based on studies that were designed in 1950s to 1960s. We are much better than that.

Vaccine development is a long and complex process, often lasting 10 to 15 years. The shortest process to-date was for the measles vaccine, which took around 8 years.

Ultimately, there are two parameters to be achieved in vaccine development – safety and efficacy. It is our hope that that a full vaccine may be developed by mid-2021.

In any aspect of public health, it is healthy to frame decision-making as a risk-benefit analysis.

- In the context of the current pandemic, the benefit of a vaccine is obviously great. It can help prevent a lot of new infections, negating the need for harsh lockdowns and mitigating its associated adverse impacts. So, under such circumstances, some appetite for risk can be expected.
- It doesn't mean that vaccine safety will be disregarded – rather, we are going to be willing to accept a vaccine based on its theoretical potential and safety track record; inferring from past evidence instead of endlessly doing experiments to achieve a certain benchmark of safety and efficacy.

Advances in vaccine development technologies can also help accelerate vaccine development. For instance, during the 2003 SARS outbreak, researchers focused solely on killed virus vaccines as it was the only technology available at that point.

Today, we have more advanced options – subunit vaccines, live-attenuated vaccines, DNA or RNA vaccines etc – which may mimic virus particles more accurately and circumvent some of the pitfalls of using killed viruses.

Another way to accelerate vaccine translation is to bring in new molecular tools to assess vaccines – using modern, genome-based approaches to analyse and postulate virulence, efficacy, antibody and T-cell response, side-effects etc.

## Vaccine Development: Collaboration with Arcturus Therapeutics

Duke-NUS Medical school has partnered with Arcturus Therapeutics, a leading messenger RNA company, to develop an mRNA vaccine for the COVID-19 virus.

mRNA vaccines direct the body's cells to express a virus protein in hopes of eliciting a robust immune response. There are several advantages to deploying mRNA formulas:

- Direct disabling of the virus – mRNA sequences may direct the translation of viral spike proteins, which are membrane proteins used by viruses to unlock host cells. Their presence in the body would elicit an immune response and thereafter, a memory response to effectively disable this crucial aspect of pathogenesis.
- Self-amplification – when mRNA vaccine molecules are delivered into host cells, it will be replicated extensively in vivo. This creates extra time for immune systems to recognise the foreign antigen and develop better memory responses. Equivalent protection may be conferred at a much lower mRNA dose.

If the clinical trials are successful, Singapore has priority to the first 5.5 million manufactured doses of the vaccine.

The trial is currently in a pre-clinical phase with ongoing animal studies. Preliminary results are reportedly promising.

## Vaccine Development: Challenges, Potential Pitfalls

Administering a SARS-CoV-2 vaccine to the community may eliminate the ability to use serology tests (which tests for antibody responses in the blood), complicating contact tracing efforts.

Future vaccine needs to be protective amongst elderly as well – paradigm shift necessary, as current vaccine development programs are mostly targeted towards younger populations. This poses additional challenges as elderly can be refractory to new vaccines – it can be hard to elicit a strong immune response from them.

Risk of antibody-dependent enhancement – when non-neutralizing antiviral proteins facilitate virus entry into host cells, leading to increased infectivity in the cells.

Extensive length of time needed for traditional vaccine development versus current need for speed and safety. For that reason, most researchers are leaning towards molecules which are already proven to be efficacious and safe.

## Vaccine Development From an Industry Perspective: Industry Approach to Advancing COVID-19 Vaccine Development and Manufacturing

Sharing of scientific data and research updates – extensive collaboration amongst all industry players (from Big Pharma to small Biotech firms); and with governments and academics as well. Working with clinical researchers and regulatory bodies to establish adaptive licensing and accelerated legislation pathways for cleared vaccine candidates.

Building manufacturing capacities in advance to reduce the lag time between Phases IV and V of vaccine development (regulatory approval and mass production); so that millions of doses can be produced and distributed within a short period of time.

Pricing issues – the industry is reportedly committed to develop a vaccine regardless of cost-effectiveness; no-holds-barred approach to pooling resources for COVID-19 vaccine development. Commitment to global access – for example, Pfizer is developing plans to establish Singapore as a COVID-19 vaccine distribution centre in order to better access other Asian populations.

Current efforts by Pfizer:

- Pfizer is currently working on various antiviral compounds which have showed some activity against SARS-CoV-2, including a partnership with the German BioNTech company to develop an mRNA vaccine.
- In a bid to share information and facilitate future research on COVID-19, the company will be sharing additional data and analysis of azithromycin via an open access review.
- Working with the Liverpool School of Tropical Medicine to research on the potential interaction between COVID-19 and the secondary bacterial pneumonia caused by Streptococcus pneumoniae.
- Looking into Janus Kinase (JAK) inhibitors – originally used for rheumatoid arthritis, but researchers are now trying to see if the molecule can provide any benefit for patients with SARS-CoV-2 interstitial pneumonia.